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Multi-pathway exposure modelling of chemicals in cosmetics with application to shampoo

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Abstract

We present a novel multi-pathway, mass balance based, fate and exposure model compatible with life cycle and high-throughput screening assessments of chemicals in cosmetic products. The exposures through product use as well as post-use emissions and environmental media were quantified based on the chemical mass originally applied via a product, multiplied by the product intake fractions (PiF, the fraction of a chemical in a product that is taken in by exposed persons) to yield intake rates. The average PiFs for the evaluated chemicals in shampoo ranged from 3×10^{-4} up to 0.3 for rapidly absorbed ingredients. Average intake rates ranged between nano- and micrograms per kilogram bodyweight per day; the order of chemical prioritization was strongly affected by the ingredient concentration in shampoo. Dermal intake and inhalation (for 20% of the evaluated chemicals) during use dominated exposure, while the skin permeation coefficient dominated the estimated uncertainties. The fraction of chemical taken in by a shampoo user often exceeded, by orders of magnitude, the aggregated fraction taken in by the population through post-use environmental emissions. Chemicals with relatively high octanol-water partitioning and/or volatility, and low molecular weight tended to have higher use stage exposure. Chemicals with low intakes during use (<1%) and subsequent high post-use emissions, however, may yield comparable intake for a member of the general population. The presented PiF based framework offers a novel and critical advancement for life cycle assessments and high-throughput exposure screening of chemicals in cosmetic products demonstrating the importance of consistent consideration of near- and far-field multi-pathway exposures.

Keywords: exposure; life cycle assessment; high-throughput screening; cosmetics; personal care products

1. Introduction

Using cosmetics can lead to consumer exposure to chemical ingredients during use or general population exposure to chemicals emitted post-use to the environment (Bergfeld et al., 2005 and Boxall et al., 2012). With limited human exposure data available for cosmetics (e.g. Koch et al., 2014), and potential for health risks associated with chemical exposures, modeling tools are needed to assess multi-pathway exposure to the variety of chemical-cosmetic combinations.

High-throughput screening (HTS) of exposures to chemicals, such as those used in cosmetics, is a risk prioritization strategy responding to the millions of product-chemical combinations on the market. In order to evaluate dozens to thousands of chemicals at a time, HTS relies on lower-tier models with high computational speed, interpretation of uncertainty, and readily available data such as national emission statistics (Isaacs et al., 2014, Shin et al., 2015 and Wambaugh et al., 2013). SHEDS-HT (Isaacs et al., 2014) for example offers a comprehensive platform for exposure screening of consumer products including cosmetics. Unlike platforms such as Crème RIFM (Safford et al., 2015) and the Targeted Risk Assessment (TRA) tool (http://www.ecetoc.org/tra) that assume dermal exposure leads to 100% dermal absorption, SHEDS-HT estimates absorption based on a simplified linear scaling of the chemical-specific skin permeation coefficient without consistently coupling all exposure pathways in a mass balance equation system (i.e. probabilistic mass transfers and exposures are forced to unity in post-processing). Skin permeation coefficients are also used in the dermal exposure models of ConsExpo (Delmaar et al., 2005) and PACEM (Delmaar et al., 2014; Dudzina et al., 2015a), which can estimate aggregated exposure fractions for

chemicals in cosmetics per unit mass of product used (Dudzina et al., 2015a) or per unit mass of chemical applied via a product (Delmaar et al., 2014). Platforms such as TRA, SHEDS-HT, ConsExpo, and PACEM can consider multiple exposure pathways and are suitable for risk-based assessment approaches. For comparative assessments based on multi-media, mass-balance exposure models (Hauschild et al., 2008; Wambaugh et al., 2013) there is a need to consistently integrate multiple exposure pathways and mechanistically consider the competition between different transfer and loss processes. For cosmetic exposure in particular, the chemical mass permeating the skin and the mass volatizing that leads to inhalation are interdependent. Accounting for simultaneous volatilization and dermal permeation has been demonstrated as an important consideration by models that focus on dermal exposure (e.g. Kasting and Miller, 2006), but is currently missing from multi-pathway exposure screening assessments. Such dermal exposure models are not suitable for implementation in HTS or life cycle assessment (LCA) because of computational complexity (e.g. requiring numeric solutions) and unsuitable exposure metrics. Furthermore, none of the aforementioned exposure models have been used to estimate post-use emissions, which lead to ubiquitous contamination of aquatic environments including sources of drinking water (Kolpin et al., 2002 and Pal et al., 2014), and subsequent environmental exposure pathways.

LCA—a common quantitative assessment technique to inform environmental risk minimization and sustainable production and consumption—generally accounts for post-use environmental emissions of cosmetic ingredients, and often assumes that a fixed fraction (e.g. 100%) of ingredients is emitted to freshwater (Koehler and Wildbolz, 2009). Life cycle impact assessment (LCIA) models used in LCA, estimate potential impacts on humans and ecosystems mediated by environmental *emissions* along product life cycle stages (e.g. manufacturing, use, disposal). Recent advances in HTS of exposures to environmental

chemicals have also employed LCIA mass balance models (Shin et al., 2015 and Wambaugh et al., 2013), thus underscoring the utility of models compatible with both HTS and LCIA despite their different goals. LCA-compatible methods to evaluate exposures occurring during product use are, however, not yet available, although exposure during use is a predominate exposure pathway for consumer products like cosmetics (Jolliet and Fantke, 2015). Recently, Jolliet et al. (2015) presented and illustrated examples of the product-specific chemical intake fraction (PiF) metric, which represents all incurred exposures per unit of chemical mass applied via a product, as the first necessary step towards developing methods for LCIA to include consumer product exposure. Models to estimate PiF have however not yet been operationalized to account for multi-pathway exposures to multiple chemicals. Existing modeling platforms are not appropriate for estimating PiF, because they are not mass balance-based across exposure pathways, they do not mechanistically account for volatilization as a competing process with dermal permeation, and they do not estimate post-use emissions and subsequent exposures. Further development of lower-tier mechanistic, mass balance-based, exposure models compatible with LCIA as well as HTS is needed to better assess potential impacts and risks related to chemical fate and exposure pathways originating from chemicals in cosmetic products (Jolliet and Fantke, 2015).

In this study, we address these research gaps and aim to (1) develop a consistent, LCA-compatible, mass balance framework coupling multi-pathway fate and exposures to chemicals in dermally applied cosmetics; (2) analyze fate and exposure pathways during and after use for an exposure duration relevant for cosmetic use; (3) quantify product intake fractions (*PiF*s) and intake rates for a case study of chemicals in a shampoo product and account for uncertainty propagation; and (4) apply the model to determine exposure to

multiple chemicals in shampoo and to identify predominant exposure pathways and data gaps.

2. Methods

2.1 Cosmetic product intake fraction framework and exposure pathways

The presented framework is applicable to non-medical, dermally-applied products regardless of their functions (e.g., beautification, hygiene, etc.), referred to as cosmetics (European Union, 2009). We built the framework based on the product intake fraction (*PiF*, Jolliet et al., 2015) metric to quantify consumer exposure to chemicals in cosmetics via use and general population exposure mediated by post-use environmental emissions (Table 1). *PiF* is defined as the fraction of the *chemical mass* applied in a cosmetic product that is eventually taken in by all exposed persons, with the dimensionless units of kilogram chemical taken in versus kilogram chemical initially applied via the cosmetic. Thereby, *PiF* accounts for exposures during the use stage that are missing in LCIA methods (Jolliet et al., 2015) which are restricted to estimating the emissions-based intake fraction, *iF* (Bennett et al., 2002). The modeling strategy for *PiF* is determined by the nature of the product (e.g. if applied on the skin), and like *iF*, model results are dependent on chemical behavior (e.g. volatility), meaning each chemical has its own *PiF* and *iF*. Consistent with *iF*, but for the amount of chemical applied rather than emitted, *PiF* multiplies the amount of chemical applied in a product to yield the human *intake* (not *uptake*) at the exposure interface—for example, permeation into the stratum corneum, not uptake into the blood stream. As the outermost epidermal barrier, stratum corneum intake is recommended for exposure assessments (Cleek and Bunge, 1993).

To preserve versatility of application and model flexibility and to enable comparison across exposure pathways, the total *PiF* (PiF^{tot}) was differentiated into five components discerning life cycle stages as well as exposure pathways and routes (indicated by superscripts); Eq. (1) follows as

$$PiF^{tot} = \underbrace{PiF^{use,d,aq} + PiF^{use,inh} + PiF^{use,d,g}}_{\text{use stage, } PiF^{use}} + \underbrace{PiF^{dis,inh} + PiF^{dis,ing}}_{\text{disposal stage, } PiF^{dis}} \quad (1)$$

Three exposure pathways were considered for the product use stage (near-field), i.e dermal permeation originating from the aqueous solution on the skin surface ($PiF^{use,d,aq}$), and if volatilized from the skin surface, inhalation ($PiF^{use,inh}$) and dermal permeation via transfer from the gaseous phase ($PiF^{use,d,g}$). Two environmentally-mediated pathways (far-field) were considered for the disposal stage (i.e. after product use), i.e. inhalation of ambient air ($PiF^{dis,inh}$) and ingestion of freshwater, fish and other food items ($PiF^{dis,ing}$), aggregated for all members of the general population. *Far-field* refers to indirect exposure to post-use emissions mediated through environmental pathways, which includes exposures via food, water, and air. *Near-field* refers to direct (dermal permeation via application on skin) and indirect (e.g. inhalation) exposures to chemical ingredients through product use. Representing all intakes by different individuals, each *PiF* component is normalized to the same initial mass of a given chemical in an applied cosmetic. Depending on the desired application of the metric, each *PiF* can be kept separate (e.g. with respect to life cycle stage, exposure route, or exposure pathway) or summed within Eq. (1).

2.2 Mass balance based models for product intake fractions

PiF was derived by first establishing the mass balance for a chemical applied via the cosmetic which advances dermal exposure models based on ConsExpo (Delmaar et al.,

2005), by including volatilization as a competing process with dermal permeation. The change in mass *m* (kg) of a chemical c remaining on the skin surface over the exposure duration *t* (h) is described in Eq. (2)

$$\frac{\mathrm{d}m_{\mathrm{c}}(t)}{\mathrm{d}t} = -\underbrace{k_{\mathrm{p,a}} \times m_{\mathrm{c}}(t)}_{\text{volatilization}} - \underbrace{k_{\mathrm{p,s}} \times m_{\mathrm{c}}(t)}_{\text{dermal intake}} \quad (2)$$

The rate constants $k_{\mathrm{p,s}}$ (h^{-1}) and $k_{\mathrm{p,a}}$ (h^{-1}) respectively account for the losses due to mass transfer from the product (p) on the skin surface to air (a) and into the stratum corneum (s) and are described in Section 2.3.

The mass fraction of chemical permeating into the skin during exposure can be expressed by the time-integrated mass of chemical intake into the stratum corneum, $m_{\mathrm{c,s}}$, divided by the initial mass of chemical applied to the skin, $m_{\mathrm{c,0}}$, shown in Eq. (3)

$$PiF^{\,\mathrm{use,d,aq}} = \frac{m_{\mathrm{c,s}}}{m_{\mathrm{c,0}}} = \frac{\int_0^{t_{\mathrm{d}}} k_{\mathrm{p,s}} \times m_{\mathrm{c}}(t) \times \mathrm{d}t}{m_{\mathrm{c,0}}} \quad (3)$$

where t_{d} is the product-specific exposure duration. Solving Eq. (2) for m_{c} and introducing into Eq. (3) yields the solution Eq. (4) (Table 1) as recently applied in Csiszar et al., (2016). The first term of Eq. (4) expresses the chemical mass fraction transferred into the skin as a competitive process between dermal intake and volatilization. The second term expresses the total fraction of mass removed from the skin surface via both volatilization and dermal intake. The fraction volatilized from the product to the air $f_{\mathrm{p,a}}$, Eq. (7) (Table 1), was derived in a similar manner to Eq. (4) and satisfying mass balance principles the sum of the fraction taken in, Eq. (4), and the fraction volatilized, Eq. (7), during use is always ≤ 1.

Table 1. Calculation of the cosmetic product intake fraction (*PiF*) for the relevant exposure pathways with respect to life cycle stages.

Life cycle stage	Exposure pathways	Equation	
use	dermal, aqueous	$PiF^{\text{use, d, aq}} = \frac{k_{\text{p,s}}}{k_{\text{p,s}} + k_{\text{p,a}}} \times \left[1 - \text{e}^{-(k_{\text{p,s}} + k_{\text{p,a}}) \times \text{t}_\text{d}}\right]$	(4)
	inhalation	$PiF^{\text{use, inh}} = f_{\text{p,a}} \times iF_{\text{a}}^{\text{inh}}$	(5)
	dermal, gas	$PiF^{\text{use, d, g}} = f_{\text{p,a}} \times iF_{\text{a}}^{\text{d, g}}$	(6)
	where	$f_{\text{p,a}} = \frac{k_{\text{p,a}}}{k_{\text{p,s}} + k_{\text{p,a}}} \times \left[1 - \text{e}^{-(k_{\text{p,s}} + k_{\text{p,a}}) \times \text{t}_\text{d}}\right]$	(7)
disposal	inhalation	$PiF^{\text{dis, inh}} = \sum_{j=1}^{n}\left(f_{\text{p},j} \times iF_j^{\text{inh}}\right)$	(8)
	ingestion	$PiF^{\text{dis, ing}} = \sum_{j=1}^{n}\left(f_{\text{p},j} \times iF_j^{\text{ing}}\right)$	(9)

$k_{\text{p,s}}$ (h^{-1}), product-to-skin transfer rate constant, is a function of the skin permeation coefficient, K_{p}^{aq} (m h^{-1}) (SI Section S1), transfer through the aqueous film, φ_{w} (m h^{-1}) (SI Section S2), and the product thickness, *h* (m), where $k_{\text{p,s}} = (h/K_{\text{p}}^{\text{aq}} + h/\varphi_{\text{w}})^{-1}$; $k_{\text{p,a}}$ (h^{-1}), product to indoor air transfer rate constant, is a function of φ_{w} (m h^{-1}) and the transfer from the aqueous film to the air, φ_{a} (m h^{-1}) (SI Section S2), and product thickness *h* (m), where $k_{\text{p},a} = (h/\varphi_{\text{a}} + h/\varphi_{\text{w}})^{-1}$; *t* (h), exposure duration prior to wash-off; $f_{\text{p,a}}$ (—), emitted fraction from the product to indoor air; $iF_{\text{a}}^{\text{inh}}$ (—), intake fraction due to inhalation of indoor air (SI eq S3a); $iF_{\text{a}}^{\text{d, g}}$ (—), intake fraction due to dermal permeation from contact with the gaseous phase in indoor air (SI eq S3b); $f_{\text{p},j}$ (—), emitted fraction from the product to environmental compartment *j* (SI Section S3), where emission to freshwater is a function of the remaining amount washed-off after use and sent to the treatment plant, $f_{\text{p,tp}} = \exp(-(k_{\text{p,s}} + k_{\text{p,a}}) \times t_{\text{d}})$; iF_j^{inh} (—), inhalation intake fraction estimated by USEtox for releases to environmental compartment *j* (SI Section S3); iF_j^{ing} (—), ingestion intake fraction estimated by USEtox for releases to environmental compartment *j* (SI Section S3).

$PiF^{use,d,g}$ and $PiF^{use,d,inh}$, Eq. (5)-(6) (Table 1) are calculated as a function of the fraction volatilized $f_{p,a}$ combined with indoor intake fractions, *iF*s (SI Section S3). Chemical removal in indoor air via sorption and degradation were not considered due to limited information and limited expected reductions in exposure (Rosenbaum et al., 2015 and Wenger et al., 2012).

Post-use (disposal stage) emission fractions are directly linked to the use stage via the conservation of mass. The fraction of chemical mass remaining on the skin surface at the end of the exposure duration was assumed to be washed-off down the household drain and thereby transferred to a conventional wastewater treatment plant, from where environmental emissions occurred according to treatment efficiency estimates (US EPA, 2012). The remaining volatilized fraction that was not taken in via inhalation or dermal permeation was assumed to be directly ventilated outdoors to urban air. The disposal stage *PiF*s, Eqs. (8)-(9) (Table 1), are a function of the emitted fraction of the applied chemical and of the far-field *iF*s (SI Section S3) capturing population-scale exposure and accounting for environmental intermedia transfers and degradation processes as estimated by USEtox 1.01 the United Nations Environment Program, Society for Environmental Toxicology and Chemistry consensus model (Hauschild et al., 2008; Rosenbaum et al., 2008).

2.3 Estimating transfer rates and skin permeation coefficient

Mass transfer from the product-to-skin and product-to-air was modeled based on the conventional two film theory where it is assumed that the steady-state transfer rate through a two-phase interface (i.e., solution-skin and solution-gas) is controlled by transfer processes specific to each phase and boundary layer and the equilibrium concentration occurs at the

interface. The overall rate constant describing transfer from the product solution to the skin, $k_{p,s}$, is a function of the rate of passage through the boundary layer of the aqueous cosmetic solution (φ_w, SI Section S2) and through the stratum corneum determined by the skin permeation coefficient (K_p^{aq}, SI Section S1), and the solution thickness, *h*. The rate constant describing transfer from the product solution to the air, $k_{p,a}$, was estimated as a two-sided boundary layer series as a function of the rate of passage through the cosmetic solution (φ_w, SI Section S2), the rate of transfer to the air based on volatility (φ_a, SI Section S2), and the solution thickness, *h*. The skin permeation coefficient K_p^{aq} is an essential consideration for dermal permeation modeling, and due to lacking empirical data we selected a QSAR to model K_p^{aq} according to the methods below.

We tested 8 QSAR models recommended for dermal exposure studies (SI Table S1) by comparing their estimated skin permeation coefficients to a list of *in vitro* human skin permeation data we compiled from the literature (Chen et al., 2010; Flynn, 1990; Hadgraft, 2002; Lian et al., 2008; Williams, 2004); these data are available in a supplementary spreadsheet described in SI Section S6. The QSARs by ten Berge, 2009 and Robinson presented by Wilschut et al., 1995 most accurately predicted the compiled *in vitro* skin permeation coefficient data among the 8 considered models (SI Table S1), both with squared geometric standard deviations of $GSD^2 \approx 20$ and standard error of SE≈0.65. The skin permeation coefficient QSARs were developed on diverse training sets, but parameterization was restricted to molecular weight (*MW*) and the octanol-water partition coefficient (K_{ow}), which contributes to the uncertainty of the QSARs. The range of suggested applicability is constrained by these parameters, e.g. 18 g/mol<*MW* <585g/mol and -3.7<log K_{ow} <5.49 (ten

244 Berge, 2009; SI Table S1), and not by other molecular descriptors (e.g. shape) or substance
245 function (e.g. surfactant).

246 **2.4 Estimating intake rates**

247 The absolute mass taken in per day by an individual product user is the product of the
248 *PiFs* and the mass of chemical initially applied. Specifically, the individual daily intake rate
249 for a product user, *IR* (μg kg^{-1} d^{-1}), in micrograms of chemical taken in per kilogram body
250 weight per day, was estimated as

251 $$IR = (PiF^{\text{use}} + PiF^{\text{dis}} \times \mathrm{N}^{\text{use}} / \mathrm{N}^{\text{pop}}) \times S_{\mathrm{c}} / \mathrm{BW} \qquad (10)$$

252 which accounts for exposures during use PiF^{use} (sum of use stage *PiF*s) and mediated by
253 post-use emissions PiF^{dis} (sum of disposal stage *PiF*s), assuming an average daily use of a
254 cosmetic by all users. Bodyweight (BW) was fixed at 70 kg $capita^{-1}$. The source of chemical
255 mass, S_{c} ($\mu g\ capita^{-1}\ d^{-1}$), was determined as the mass of cosmetic product applied per
256 person per day, S_{P} (kg $capita^{-1}$ d^{-1}), multiplied by the concentration (*w/w*) of chemical in the
257 product, f_{c} ($\mu g\ kg^{-1}$). To obtain the individual average dose taken in from the disposal of
258 product used, PiF^{dis} must be multiplied by the fraction of the population using the product, i.e
259 the ratio of the total number of product users to the overall receptor population size
260 considered in the PiF^{dis} calculation ($\mathrm{N}^{\text{use}} / \mathrm{N}^{\text{pop}}$).

261 **2.5 Shampoo case study**

262 The *PiF* equations listed in Table 1 were determined for a case study product and
263 chemical ingredients. Shampoo was selected for a case study on a commonly used cosmetic,
264 washed-off directly after use. Ingredients and formulation vary greatly, e.g., pH 3-9
265 (Gavazzoni Dias et al., 2014 and Goldsmith et al., 2014). Shampoo is typically >2/3 water

266 and subsequently diluted six-fold during use (Bremmer, et al., 2006). Five exemplary
267 chemicals were first selected from the CPCat (Dionisio et al., 2015) or Household Products
268 (http://householdproducts.nlm.nih.gov) databases. Chemicals were selected to span a
269 representative range of physicochemical properties (i.e. molecular weight, octanol- and air-
270 water partition coefficients) (SI Figure S2) to demonstrate model behavior, and toxicological
271 relevance was not a selection criterion. The selected chemicals by name and by Chemical
272 Abstracts Service (CAS) number were: benzyl benzoate (CAS 120-51-4), isopropyl alcohol
273 (CAS 67-63-0), propylene glycol (CAS 57-55-6), sodium lauryl sulfate (CAS 151-21-3), and
274 quinoline yellow (CAS 8004-92-0). Average concentrations of these chemicals in shampoo
275 were reported (Bremmer et al., 2006 and Goldsmith et al., 2014) below water saturation as
276 indicated in the USEtox 1.01 database. *PiF* was evaluated based on an average use scenario
277 (SI Table S2) for men and women with an exposure duration of 4 minutes (0.065 h), after
278 which the solution is washed-off (Bremmer et al., 2006, Hall et al., 2007 and Loretz et al.,
279 2006).

280 To characterize ranges in *PiF* estimates for a larger number of substances, we also
281 identified 414 additional chemicals based on inquiry of "personal_care cosmetics shampoo"
282 within the CPCat database (Dionisio et al., 2015). We then obtained all the chemical-specific
283 parameters required for both the near- and far-field models by using the USEtox 1.01
284 substance database (downloadable at http://usetox.org). The properties required for the near-
285 field *PiF* models, Eqs. (4)-(7), are MW, Kow, Kaw, and the properties required for the far-
286 field *iF* model are listed in the USEtox documentation. The resulting list of 118 chemicals
287 was then restricted to the applicability range of the skin permeation QSAR model (ten Berge,
288 2009), 18 g/mol<MW<585 g/mol and -3.7<log Kow<5.49. The wastewater treatment plant
289 efficiencies were extracted for each chemical when available in STPWIN (EPI Suite v4.11),

290 and then combined with the USEtox far field intake fractions, *iF*, to estimate the far-field *PiF*
291 based on post-use environmental emissions (Eqs. (8)-(9); SI section S3). The remaining 69
292 chemicals (listed in the supplementary spreadsheet described in SI S-6) spanned the QSAR
293 applicability range for physicochemical properties offering a robust case study of model
294 behavior. Additional chemicals could be modeled if their required properties are obtained
295 (e.g. from EPI Suite). In addition to *PiFs*, *IRs* were estimated when the chemical
296 concentrations in shampoo ($\mu g\ kg^{-1}$) were available in Goldsmith et al., 2014 and non-zero
297 values were averaged; 53 chemicals had sufficient data to estimate *IR*s. Benzyl benzoate
298 concentration was unavailable and was thus estimated from the shampoo preservative
299 concentration range (Bremmer, et al., 2006). The number of daily users was set equivalent to
300 the USEtox 1.01 continental population of 1 billion people thus $N^{use}/N^{pop}=1$ in Eq. (10).

301 **2.6 Sensitivity, uncertainty, and variability analyses**

302 To identify potentially important parameters, model sensitivity was evaluated for the
303 values of PiF^{use} for all chemicals, as the change in the resulting model output divided by the
304 change in an input parameter, fixed at 10%, with all other parameters fixed. Further, the
305 uncertainty distribution of product intake fractions as estimated by Eqs. (4)-(9) (Table 1)
306 were determined using a Monte Carlo (MC) simulation in Matlab® based on 10^6 randomly
307 permutated points for each parameter considering log-normal distributions except for room
308 ventilation (McKone and Bogen, 1992) (SI Table S2 and Section S4). Uncertainty was also
309 estimated with respect to environmental fate and intake fractions (SI Section S4). MC
310 determines the stochastic propagation of parameter uncertainty and variability, and was also
311 used to evaluate the contribution of parameters to the overall distribution. We further
312 investigated variability with respect to the exposure duration and the distribution of shampoo

mass typically applied by consumers (Hall et al., 2007) whereas the average concentration of chemicals in shampoo was fixed, due to a lack of data on realistic concentration distributions. Results are therefore indicative of intake rates for the considered concentrations, whereas *PiF*s are concentration independent.

2.1 Results

3.1 Use stage exposure to chemicals in shampoo

PiF^{use} and relative contributions of exposure pathways varied greatly for the five chemicals studied, ranging in total from ≈0.0003 (quinoline yellow) to ≈0.3 (benzyl benzoate) with the dimensionless units of kilogram chemical taken in versus kilogram chemical initially applied in shampoo. Due to $K_{ow}>10^3$ and $K_{aw}>10^{-3}$, relatively fast transfer rates to skin and to air >1 h^{-1} were estimated for benzyl benzoate, resulting in rapid use stage intake and a high PiF^{use} >0.1, despite the short shampoo exposure duration of 4 minutes (0.065 h) (Bremmer et al., 2006). Considering the high volatility of isopropyl alcohol and minimal dermal intake associated with $K_{ow}\approx 1$, $PiF^{use,inh}$ is high (3.3×10^{-2}) and superior to $PiF^{use,d,aq}$. Sodium lauryl sulfate and quinoline yellow, with K_{ow} <100, MW>200 (g mol^{-1}) and negligible volatility with a $K_{aw}<10^{-10}$, were estimated to have low-end exposure during use (PiF^{use} <0.001).

3.2 Influence of exposure duration on exposure and post-use emissions

As demonstrated in Figure 1A-D, PiF^{use} is a function of exposure duration (0-10 h). For volatile case study chemicals (i.e. benzyl benzoate and isopropyl alcohol), an exposure duration exceeding one hour does not influence PiF^{use} any further; after this point, the chemical on the skin surface has been completely removed from the skin surface via volatilization and dermal permeation. For such chemicals, our modeling predicts that a

maximum PiF^{use} occurs within an hour and plateaued well below 1 (e.g. 0.3) (see Figure 1D). In contrast, other compounds with lower volatility, such as sodium lauryl sulfate, quinoline yellow or propylene glycol, can potentially approach *PiF*=1 intake if they remain on the skin for an extended duration (i.e. >10 h). Figure 1E-H also demonstrate that post-use emissions are a direct function of the fate and exposures during the use stage which is especially important to consider for chemicals with fast skin permeation and/or volatility. Post-use emissions also influence the exposure pathways in the far-field as demonstrated in Figure G-H for ingestion due to emission to freshwater and inhalation due to emission to urban air.

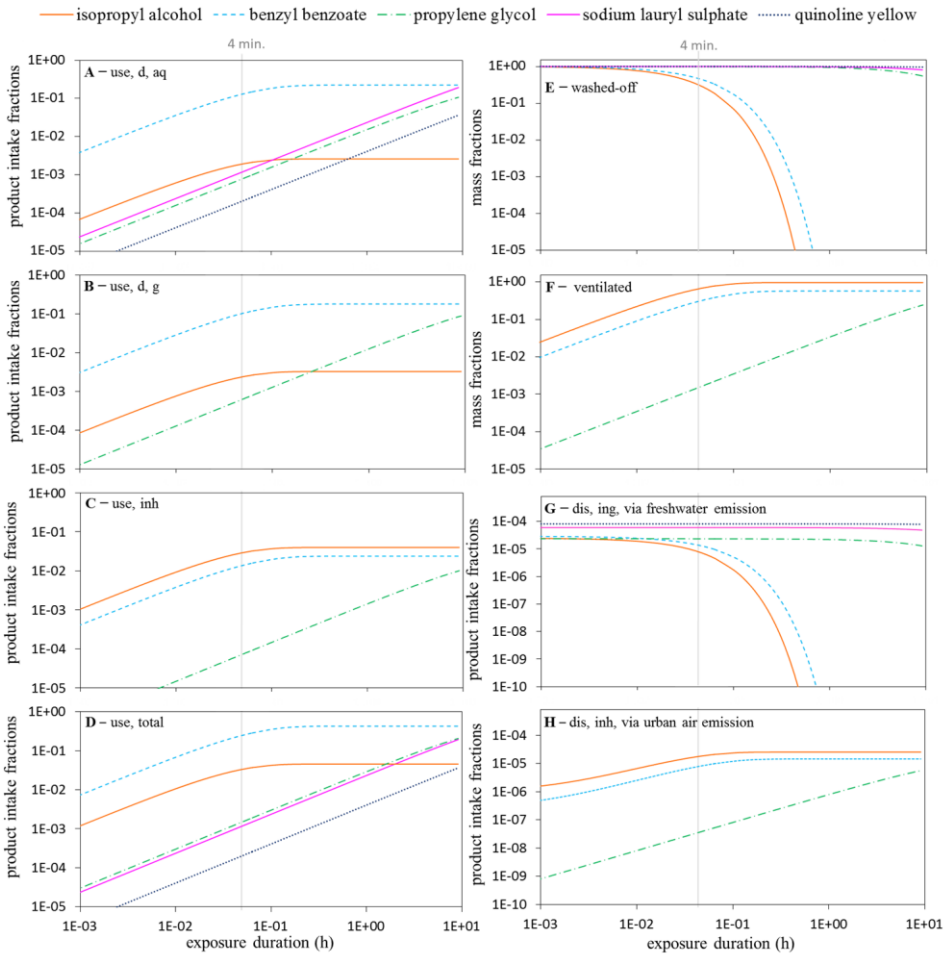


Figure 1 A-H. Evolution of use stage product intake fractions through the exposure duration for (A) dermal take of the aqueous solution on the skin, (B) dermal intake of the gaseous phase, and (C) inhalation of the gaseous phase, and (D) the sum of all use stage routes (A-C). Evolution of post-use emissions and disposal stage product intake fractions as a result of the exposure duration during use for (E) wash-off to the wastewater treatment plant, $f_{p,tp}$, (F) ventilated to urban air, $f_{p,a}$, (G) ingestion via foods and water due to emissions to freshwater (H) inhalation due to emissions to urban air. The grey vertical line represents the shampoo case study exposure duration of 0.065 hours (i.e. 4 minutes).

3.3 Comparison between use and disposal stage exposures

Main results and model parameters are presented in Table 2, with further details provided in SI Tables S2-4. Estimated *PiF*s for all exposure pathways (Figure 2) demonstrated that in most cases PiF^{use} dominated. However, when considering uncertainty, quinoline yellow had PiF^{dis} close to $PiF^{use} \approx 10^{-4}$, predominated by ingestion of drinking water. By definition, PiF^{dis} is always a function post-use emissions (SI Section S3). Thereby when consumer exposure is low, (e.g. <0.001) the post-use emission fraction approaches 1, and the magnitude of PiF^{dis} is only controlled by the far-field intake fraction, *iF* (Rosenbaum et al., 2008). Near- and far-field models shared mechanistic basis on physicochemical properties (K_{ow}, $K_{aw,}$ MW), therefore chemicals with PiF^{use} >0.1 attributable to a high K_{ow} may in addition have a relatively high environmental *iF* of emissions, e.g. $>10^{-4}$ due to bioaccumulation in the food chain.

370

371 Table 2. Physicochemical properties, key model parameters, and resulting product intake
372 fractions and individual intake rates for a user using a shampoo containing the five exemplary
373 chemicals.

Variable	Unit	benzyl benzoate	isopropyl alcohol	propylene glycol	sodium lauryl sulfate	quinoline yellow
MW	g mol^{-1}	212.3	60.1	76.1	288.38	353.35
K_{ow}	–	9.3×10^{3}	1.1	0.12	40	11
K_{aw}	–	3.0×10^{-4}	5.8×10^{-4}	9.2×10^{-7}	4.9×10^{-16}	7.5×10^{-17}
f_c	μg kg^{-1}	1.5×10^{3}	1.0×10^{7}	9.8×10^{7}	4.7×10^{7}	2.8×10^{6}
$k_{p,s}$	h^{-1}	3.9	6.9×10^{-2}	1.6×10^{-2}	2.4×10^{-2}	4.1×10^{-3}
$k_{p,a}$	h^{-1}	13	26	5.0×10^{-2}	2.6×10^{-11}	4.1×10^{-12}
$f_{p,a}$	–	0.53	0.82	3.2×10^{-3}	1.7×10^{-12}	2.6×10^{-13}
$f_{p,tp}$	–	0.32	0.18	0.99	0.99	1.0
iF_a^{inh}	–	3.1×10^{-2}	4.0×10^{-2}	3.0×10^{-2}	1.7×10^{-2}	1.7×10^{-2}
$iF_a^{d,g}$	–	0.23	3.3×10^{-3}	0.26	0.59	0.59
$PiF^{use,d,aq}$	–	0.15	2.1×10^{-3}	1.0×10^{-3}	1.5×10^{-3}	2.7×10^{-4}
$PiF^{use,d,g}$	–	0.12	2.7×10^{-3}	8.5×10^{-4}	1.0×10^{-12}	1.5×10^{-13}
$PiF^{use,inh}$	–	1.6×10^{-2}	3.3×10^{-2}	9.5×10^{-5}	2.8×10^{-14}	4.4×10^{-15}
$PiF^{dis,inh}$	–	9.9×10^{-6}	2.1×10^{-5}	5.3×10^{-8}	2.5×10^{-9}	2.9×10^{-18}
$PiF^{dis,ing}$	–	1.9×10^{-5}	5.5×10^{-6}	2.4×10^{-5}	6.0×10^{-5}	8.1×10^{-5}
PiF^{total}	–	0.29	3.8×10^{-2}	2.0×10^{-3}	1.6×10^{-3}	3.5×10^{-4}
IR	μg kg^{-1} d^{-1}	3.1×10^{-2}	27	14	5.4	7.0×10^{-2}

Grey shading indicates greater than 10% relative contribution to total *PiF*; *MW*, molecular weight; K_{ow}, octanol-water partition coefficient; K_{aw}, air-water partition coefficient, adjusted for average skin temperature of 34 °C (SI Section S2); f_c, fraction of chemical originally in shampoo; $k_{p,s}$, product to skin transfer rate constant; $k_{p,a}$, product to air transfer rate constant; $f_{p,a}$, fraction volatilized from product to indoor air, dimensionless units of kilogram chemical emitted to indoor air per kilogram chemical initially applied; $f_{p,tp}$, fraction transferred from product to wastewater treatment plant, dimensionless units of kilogram chemical transferred to treatment plant per kilogram chemical initially applied; iF_a^{inh}, indoor air intake fraction due to inhalation and $iF_a^{d,g}$, indoor air intake fraction due to dermal contact with volatilized gas-phase chemicals, both with dimensionless units of kilogram taken in per kilogram emitted indoors to the shower stall; all *PiF*s (see Table 1) have dimensionless units of kilogram chemical taken in versus kilogram chemical initially applied; *IR*, intake rate as a function of *PiF* and mass applied. The disposal (dis) stage *PiF*s are aggregated for all emission compartments (emissions to air, water, and soil).

3.4 Sensitivity, variability, and uncertainty

Monte Carlo (MC) simulations accounting for uncertainty and variability according to parameter distributions within SI Table S2, demonstrated that PiF^{use} varied by one to three orders of magnitude, with an upper limit of $PiF \leq 1$ due to mass balance principles (see 95th CI, Figure 2). Due to non-linearity, sensitivity on PiF^{use} was chemical-specific but the case study chemicals were usually most sensitive to the skin permeation coefficient, except for benzyl benzoate with the highest estimated K_p^{aq} ($>10^{-4}$ m h^{-1}) which was most sensitive to the thickness of the solution applied on the skin surface and the resistance of the aqueous boundary layer. Further investigation of K_p^{aq}'s role in the propagated results distribution can be found with SI Figures S3-4. The influence of K_p^{aq} emphasizes the importance of obtaining good quality experimental data or at least selecting the best available predictive model, i.e the QSARs by ten Berge (2009) or Robinson presented by Wilschut et al. (1995). When removing variabilities in consumer behaviors and use scenarios (exposure duration, mass applied, body surface areas, indoor ventilation rates, breathing rates) the 95% CI interval was

reduced by 16-22% for all example chemicals but for benzyl benzoate for which only a 4% change was seen (difference between Figure 2, where all uncertainties and variabilities are accounted for, and SI Figure S5 where only uncertainties on estimated parameters are considered).

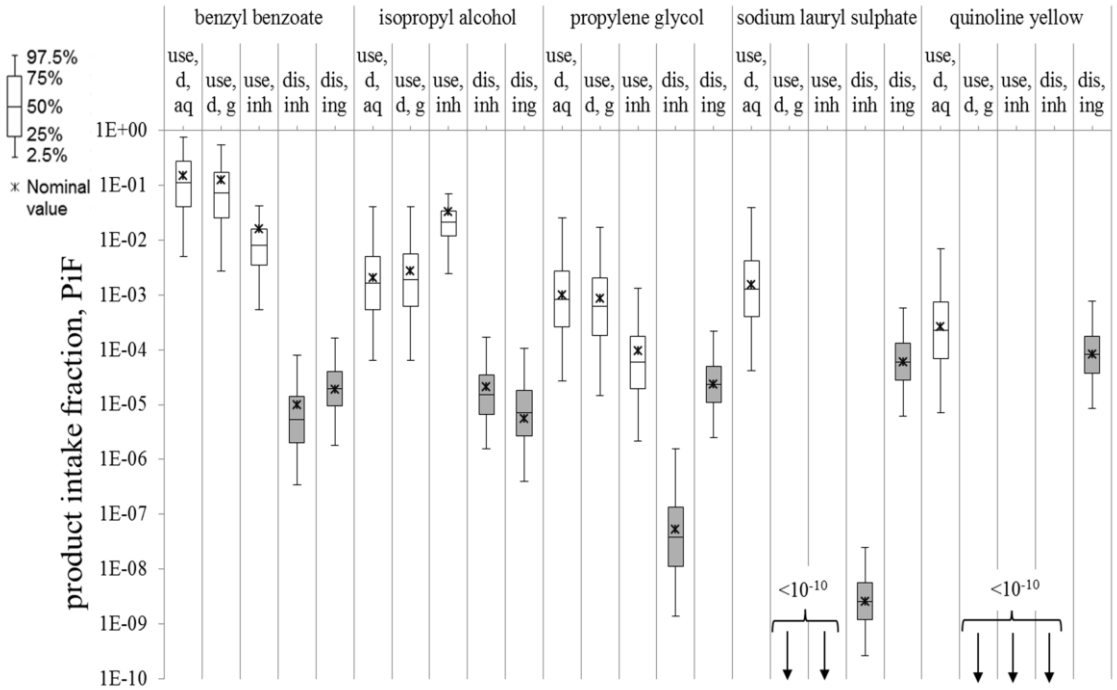
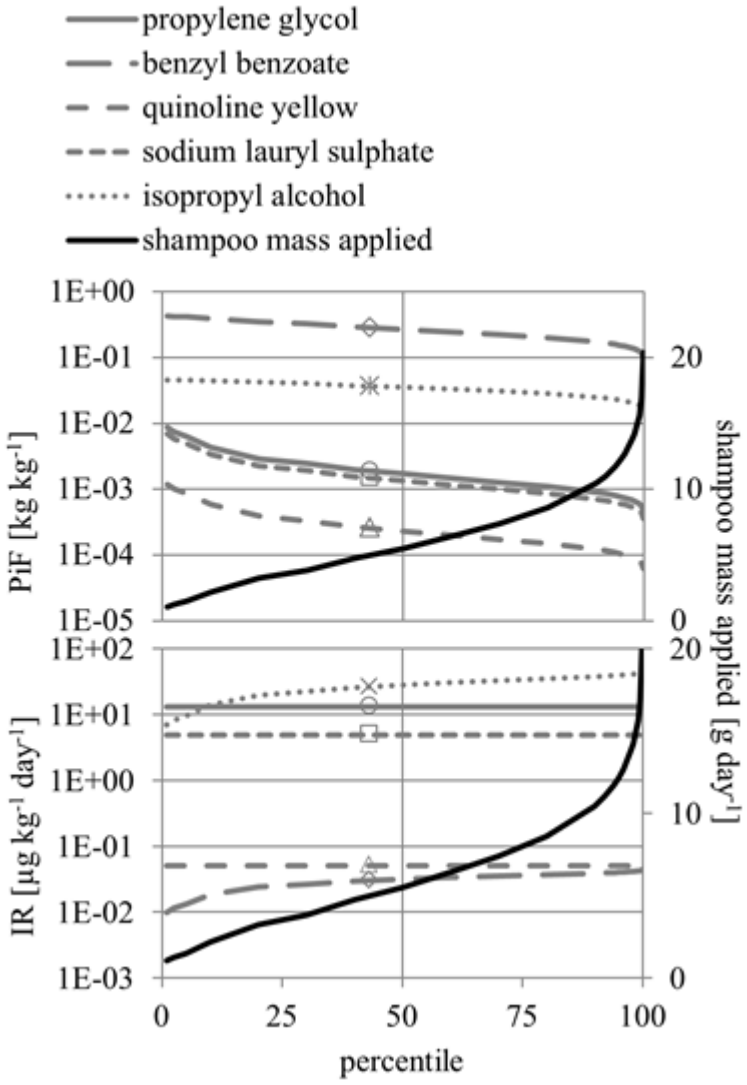


Figure 2. Ranges of PiF^{use} (white) and PiF^{dis} (grey) for the considered exposure pathways and routes: use stage dermal permeation due to the aqueous solution on the skin surface (use, d, aq) and due to the gaseous phase (use, d, g), inhalation (inh), and ingestion (ing) both during the use stage and due to the disposal (dis) stage (via post-use emissions). Calculated values (based on means of input variables) are marked with a star.

3.5 Intake Rates

PiF is multiplied by the chemical mass applied to estimate *IRs* for an individual product user, see Eq. (9), and the chemical mass applied is estimated as the product of the mass of shampoo applied and the fraction of chemical mass f_c ($\mu g\ kg^{-1}$) in the shampoo

417 (Table 2). We found *IR* for shampoo applications of these five chemicals was on the order of
418 nano- to several micrograms chemical intake per kilogram bodyweight per day, which is
419 similar to other recent estimates (Delmaar et al., 2014, Dudzina et al., 2015a and Safford et
420 al., 2015). Conservatively assuming that the number of product users was equal to the
421 number of individuals in a population, we found that for the 53 chemicals with readily
422 available data to estimate *IR*s in this study, the contribution of the far-field *IR* was a function
423 of the magnitude of the near-field exposure; for example when the near-field *PiF* was greater
424 than 0.01, the far-field exposure negligibly contributed to *IR* (<1%). The near- and far-field
425 exposures contributed to 70% and 30% of the total intake rate of 0.07 ($\mu g\ kg^{-1}\ d^{-1}$) for
426 quinoline yellow, respectively. Accounting for uncertainty ranges, these contributions were
427 not significantly different.
428 Figure 3 demonstrates that the order of chemical prioritization changed when
429 considering the ranking of *IR* compared to *PiF*. For example, benzyl benzoate had the highest
430 *PiF*, but resulted in the lowest *IR* due to the assumed low concentration fraction in shampoo
431 for such preservatives (0.00015%) (Bremmer et al., 2006). Increasing the mass of shampoo
432 used across the range typically applied by consumers (Hall et al., 2007) resulted in decreasing
433 *PiF* by approximately an order of magnitude due to a thicker solution on skin surface (when
434 the applied surface area is assumed constant). However, *IR* remained relatively stable because
435 the effects of increasing the mass of chemical applied were compensated by the decreasing
436 *PiF*.
437



438

439 Figure 3. Total *PiF* and *IR* based on percentiles of shampoo mass applied (black solid line).

440 Symbols indicate the calculated values based on the mean mass applied daily (5.05 g d^{-1}).

441 **3.6 Screening of additional chemicals**

442 Figure 4 shows the range in *PiF*s evaluated for the 69 chemicals in shampoo that had data

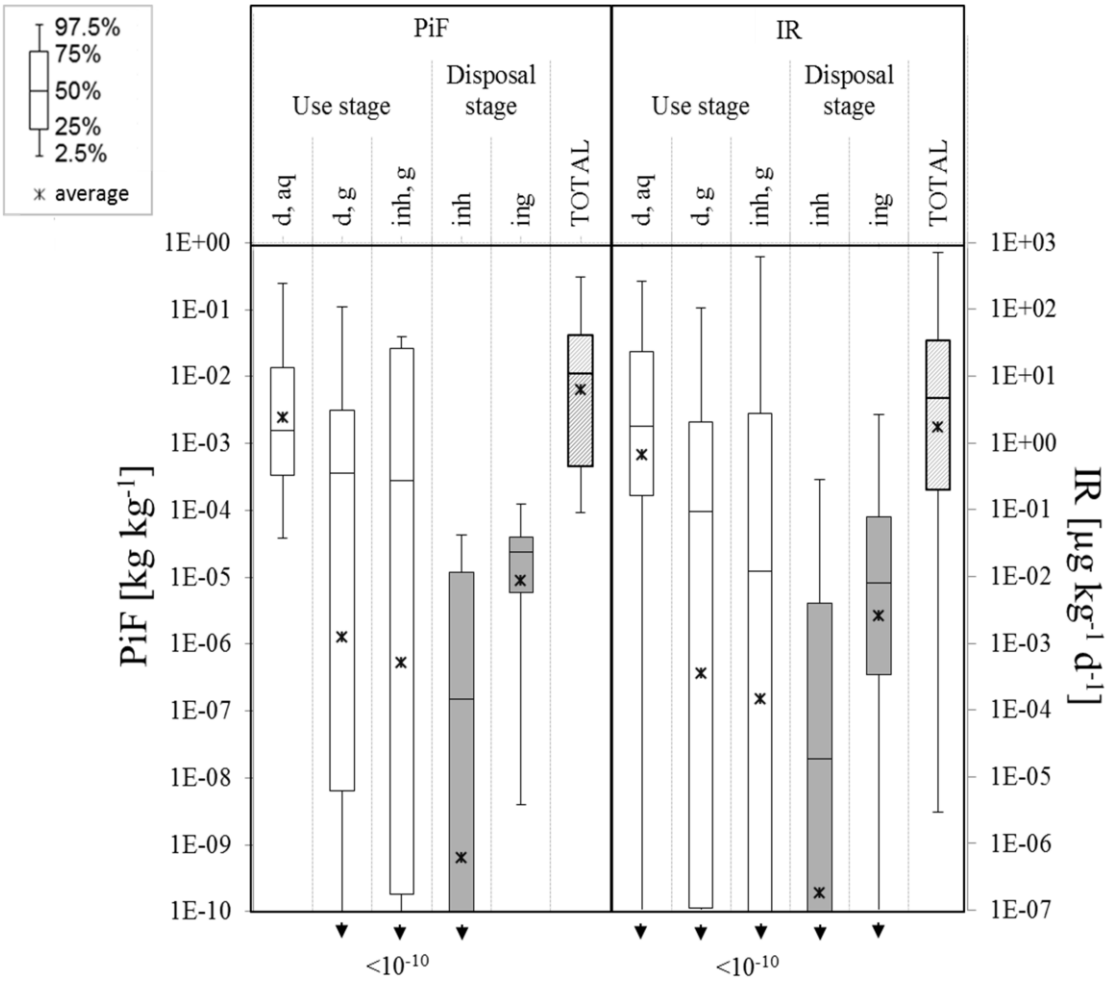
443 readily available to enable screening. Direct dermal intake generally dominates exposure, but

444 inhalation was greater than dermal permeation for 16 out of the 69 evaluated chemicals.

445 These chemicals typically have a smaller octanol-air partition coefficient, K_{oa}, with log values

446 between −1 and 6.5, versus 3.5 and 32.5 for chemicals where direct dermal exposure

447 dominated. Four chemicals had disposal stage *PiF*s greater than use stage *PiF*s (SI Figure
448 S6).
449



450
451 Figure 4. Product intake fraction (*PiF*) and intake rate ranges (*IR*) for a subset of chemicals
452 found in shampoo (n=69). Stars indicate geometric means across chemicals.
453

2.2 Discussion

4.1 Feasibility and Limitations

With a lack of empirical data on cosmetic exposure there have been many recent modeling attempts. Generally, our dermal exposure results fall in the same range, or even predict the same values to one significant digit, of other recent exposure models built on empirical evidence. For instance, a PACEM case study using the dermal exposure equation in Delmaar et al., 2005 predicted an exposure fraction of 0.02 for diethyl phthalate (DEP) in shampoo (Delmaar et al., 2014). Using our model, which added simultaneous volatilization to the Delmaar et al., 2005 equation, a value of $PiF^{use,d,aq}$=0.02 for DEP in shampoo was also obtained. Although generally important to consider for volatile or semi-volatile compounds, the low volatility of DEP led to negligible competition with dermal permeation, resulting in similar dermal exposure estimates to Delmaar et al., 2014. We also compared our dermal exposure and volatilization results with the Center for Disease Control (CDC) Finite Dose Skin Permeation Calculator which is based on a different mass balance approach but also uses physicochemical properties to estimate skin permeation and volatilization (Dancik et al., 2013 and Kasting and Miller, 2006). Using vapor pressures from 0.22-0.66 Pa (range from 25-32 ^{o}C) (US EPA, 2012) for DEP and a 6x dilution with water, the CDC model predicted a relatively low fraction of 1-3% of the original mass has volatilized after 4 minutes (the shampoo exposure duration), without water dilution the CDC model predicts DEP volatilization between 3-10%. Our model predicted comparable fraction emitted to indoor air $f_{p,a}$ ≈5%. The CDC model has a different configuration from our model which complicates comparison for dermal exposure, for example the model assumes immediate uptake into the upper layers of the stratum corneum and volatilization and deeper permeation occurs from there (Kasting and Miller, 2006). Generally, inhalation is considered negligible

for dermally applied cosmetics with limited experimental verification of this assumption; our model predicted that inhalation can be an important exposure pathway for volatile chemicals applied dermally and this is corroborated with recent experimental evidence (Biesterbos et al., 2015; Dudzina et al., 2015b). Also recently, Csiszar et al., (2016) used Eq. (4) to estimate dermal exposure to parabens and modeled results compared reasonably well with national biomonitoring data, bolstering the feasibility of modeling approaches.

Through a Monte Carlo simulation, we estimated the propagation of uncertainty related to the parameters within the model set-up, and corroborated that the skin permeation coefficient, K_p^{aq}, is a main contributor to uncertainty in dermal exposure modeling (Bouwman et al., 2008). As a concentration-independent and steady-state approximation, the K_p^{aq} metric, which we estimated by QSAR, does not consider mixture effects (Megrab et al., 1995), thermodynamics (Williams and Barry, 2012), or non-steady-state dynamics resulting in faster intake into the stratum corneum at short exposure durations (ten Berge, 2009, Cleek and Bunge, 1993 and Grégoire et al., 2009). Furthermore, mixture formulations affect dermal permeation in a variety of ways. As commonly occurring examples for cosmetics, co-solvents, terpenes and surfactants can *increase* the flux of dermal chemical intake in comparison to aqueous solutions, for example due to thermodynamic alterations or disruption of the skin's natural permeability (Williams and Barry, 2012). Co-solvents specifically can increase solution concentrations above water saturation, which leads to higher mass transfer into the skin than occurring at maximum water concentration (Moser et al., 2001). In contrast, emulsions, crystallization and ionization can potentially *decrease* flux, e.g., due to partitioning out of the aqueous phase and adjustment of the effective K_{ow} (Grégoire et al., 2009 and Moser et al., 2001). 16 out of the 69 chemicals screened had concentrations in the

shampoo solution (even when considering 6x dilution) exceeding water saturation, indicating the presence of a co-solvent. Due to the uncertainty regarding saturation and co-solvent effects, these chemicals were flagged in the supplementary spreadsheet described in SI Section S6, and the saturation concentrations were included for reference. Furthermore, 17 out of the 69 of the chemicals in the extended shampoo case study had dissociation constants indicating potential ionization, and these chemicals are also flagged in the supplementary spreadsheet described in SI Section S6. Empirical and modeling studies to date generally limit focus to a subset of these effects and how they influence K_p^{aq} (Grégoire et al., 2009, Megrab et al., 1995 and Moser et al., 2001). Paradoxically, parameterizing K_p^{aq} models (e.g. QSARs) with respect to various formulation variables such as ionization may only partially resolve the uncertainty, which largely results from natural variation in skin and from difficult-to-estimate contributions, e.g. related to three-dimensional molecular shape (Akomeah et al., 2007, Cruciani et al., 2000 and Tadros et al., 2004).

Monte Carlo only considers the propagation of uncertainties of model parameters. For example, removal processes within indoor air were not parameterized in the model and therefore did not contribute to uncertainty distribution as estimated via Monte Carlo. The volatile compounds within the case study (benzyl benzoate, isopropyl alcohol) do not have ozone or nitrate degradation rates available to our knowledge (US EPA, 2012, Wenger et al., 2012) and sorption to surfaces within the bathroom or shower stall is likely limited (Won et al., 2001). Due to these data gaps removal processes within indoor air were not parameterized within our model but indoor degradation is unlikely to increase the removal rate by more than 20% (Rosenbaum et al., 2015) which could have an effect for chemicals with high inhalation. Additionally, the developed mass balance model was based on several assumptions, for

example that the thickness of the cosmetic on the skin was constant. In reality, some cosmetics formulations or long exposure durations may result in volatilization that substantially decreases the thickness on the skin surface, resulting in an increase of thermodynamic activity leading to increased dermal transfer, assuming no crystallization (Moser et al., 2001).

With significant hurdles to account mechanistically for the multitude of formulation effects, at least within lower-tier models appropriate for HTS and LCIA, a qualitative descriptor to identify chemical functions (e.g. surfactant, co-solvent) is an emerging, resourceful way forward to improve HTS of dermal exposure to cosmetics (Chevillotte et al., 2014). Additionally, as cosmetics may be intentionally formulated with specific properties to enhance or inhibit skin permeation, industrial knowledge may bring significant benefits to modeling improvements. The *PiF*-based framework presented in this study (Table 1) offers a novel and critical advancement to LCIA and HTS by building on accessible dermal exposure research, and offers a flexible framework which may be updated to account for improvements in dermal research, e.g. improved estimates of mass transfers in cosmetic mixtures.

4.2 Implications and future work

In this study, mass balance models enabled connecting, quantifying and comparing near- and-far-field contributions to the product intake fraction (*PiF*) (Jolliet et al., 2015). The *PiF* framework is compatible with the *iF*-based framework established within the LCIA step of LCA. An example application in LCA is detailed in SI Section S5. The results of the shampoo case study corroborated the intuition that exposure during use of a cosmetic usually exceeds environmental exposures to post-use emissions of the product, at least for product users, and justifies including use stage exposure in LCIA of cosmetic products. Furthermore,

548 results demonstrated the importance of bridging, and simultaneously considering, multi-
549 pathway exposures on a mass balance basis, as inhalation during use dominated over dermal
550 intake for 20% of chemicals in the extended shampoo case study, and post-use far-field
551 exposures can be comparable to exposure during use for chemicals with low permeation
552 coefficients and high washed-off fractions. Such observations are a direct consequence of
553 mechanistic consideration of physicochemical properties within the models and their
554 connection on a mass balance basis. The chemicals considered in this study had a range of
555 functions including fragrances, surfactants, and preservatives and physicochemical
556 properties, but they cover only a fraction (<20%) of chemicals known to occur in shampoo
557 (Dionisio et al., 2015). Complementary studies are therefore needed to systematically
558 investigate the role of physicochemical properties in determining the magnitude of various
559 exposure pathways, and emission magnitudes. SI Section S5 illustrates in a proof of concept
560 case study how our models can be integrated and applied in an LCIA framework. It also
561 shows that accounting for volatilization of volatile substances can lower the estimated
562 ecotoxicity impacts by orders of magnitude when compared to the common conservative
563 assumption of 100% washed-off to freshwater after use. With consideration of the limitations
564 and strengths, the presented framework is deemed best applicable for future assessments that
565 aim to compare relative magnitudes of population-scale chemical intakes, e.g. in LCA to
566 support estimation of impact trade-offs or in HTS of exposures to prioritize chemicals and
567 product combinations of concern.
568 Some of the greatest limitations to HTS and LCIA of cosmetics are data availability,
569 both for model development and validation and uncertainty. Fortunately, recent works have
570 focused on compiling lists of chemicals in cosmetics and consumer products (Dionisio et al.,
571 2015), concentrations in cosmetics (Goldsmith et al., 2014), and cosmetic use patterns

(Comiskey et al., 2015) making HTS of exposures increasingly feasible. Despite efforts to estimate exposure, LCIA and risk-based HTS remain limited by the number of chemicals that have compiled toxicity information underscoring the importance of complementary research on high-throughput assays of bioactivity (Wetmore et al., 2015) and also implies an urgent need to mandate publically funded "open-access" platforms with toxicity information, such as TOXNET (http://toxnet.nlm.nih.gov/) and REACH dossiers (http://echa.europa.eu/), to be offered in more usable forms (e.g. spreadsheets).

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Supporting Information Available

Supporting information includes detailed equations, supplementary results, and a supplementary spreadsheet with all calculations as well as *in vitro* skin permeation data.

References

Akomeah, F.K., Martin, G.P., Brown, M.B., 2007. Variability in human skin permeability in vitro: Comparing penetrants with different physicochemical properties. J. Pharm. Sci. 96, 824–834. doi:10.1002/jps.20773

Bennett, D.H., McKone, T.E., Evans, J.S., Nazaroff, W.W., Margni, M.D., Jolliet, O., Smith, K.R., 2002. Peer Reviewed: Defining Intake Fraction. Env. Sci Technol 36, 206A–211A. doi:10.1021/es0222770

Berge ten, W., 2009. A simple dermal absorption model: Derivation and application. Chemosphere 75, 1440–1445. doi:10.1016/j.chemosphere.2009.02.043

Bergfeld, W.F., Belsito, D.V., Marks Jr., J.G., Andersen, F.A., 2005. Safety of ingredients used in cosmetics. J. Am. Acad. Dermatol. 52, 125–132. doi:10.1016/j.jaad.2004.07.066

Biesterbos, J.W.H., Beckmann, G., van Wel, L., Anzion, R.B.M., von Goetz, N., Dudzina, T., Roeleveld, N., Ragas, A.M.J., Russel, F.G.M., Scheepers, P.T.J., 2015. Aggregate dermal exposure to cyclic siloxanes in personal care products: Implications for risk assessment. Environ. Int. 74, 231–239. doi:10.1016/j.envint.2014.10.017

Bouwman, T., Cronin, M.T.D., Bessems, J.G.M., Sandt, J. van de, 2008. Improving the applicability of (Q)SARs for percutaneous penetration in regulatory risk assessment. Hum. Exp. Toxicol. 27, 269–276. doi:10.1177/0960327107085829

Boxall, A.B.A., Rudd, M.A., Brooks, B.W., Caldwell, D.J., Choi, K., Hickmann, S., Innes, E., Ostapyk, K., Staveley, J.P., Verslycke, T., Ankley, G.T., Beazley, K.F., Belanger, S.E., Berninger, J.P., Carriquiriborde, P., Coors, A., DeLeo, P.C., Dyer, S.D., Ericson, J.F., Gagne, F., Giesy, J.P., Gouin, T., Hallstrom, L., Karlsson, M.V., Larsson, D.G.J., Lazorchak, J.M., Mastrocco, F., McLaughlin, A., McMaster, M.E., Meyerhoff, R.D., Moore, R., Parrott, J.L., Snape, J.R., Murray-Smith, R., Servos, M.R., Sibley, P.K., Straub, J.O., Szabo, N.D., Topp, E., Tetreault, G.R., Trudeau, V.L., Van Der Kraak, G., 2012. Pharmaceuticals and Personal Care Products in the Environment: What Are the Big Questions? Environ. Health Perspect. 120, 1221–1229. doi:10.1289/ehp.1104477

Bremmer, HJ, LCH, P. de L., van, E.J., 2006. Cosmetics Fact Sheet. To assess the risks for the consumer. Updated version for ConsExpo 4 [WWW Document]. URL http://rivm.openrepository.com/rivm/handle/10029/7305 (accessed 7.23.12).

Chen, L., Lian, G., Han, L., 2010. Modeling transdermal permeation. Part I. Predicting skin permeability of both hydrophobic and hydrophilic solutes. AIChE J. 56, 1136–1146. doi:10.1002/aic.12048

Chevillotte, G., Ficheux, A.S., Morisset, T., Roudot, A.C., 2014. Exposure method development for risk assessment to cosmetic products using a standard composition. Food Chem. Toxicol. 68, 108–116. doi:10.1016/j.fct.2014.03.010

Cleek, R.L., Bunge, A.L., 1993. A New Method for Estimating Dermal Absorption from Chemical Exposure. 1. General Approach. Pharm. Res. 10, 497–506. doi:10.1023/A:1018981515480

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to

639 fragrance ingredients in cosmetics and personal care products. Regul. Toxicol.
640 Pharmacol. 72, 660–672. doi:10.1016/j.yrtph.2015.05.012
641 Cruciani, G., Crivori, P., Carrupt, P.-A., Testa, B., 2000. Molecular fields in quantitative
642 structure–permeation relationships: the VolSurf approach. J. Mol. Struct.
643 THEOCHEM 503, 17–30. doi:10.1016/S0166-1280(99)00360-7
644 Csiszar, S.A., Ernstoff, A.S., Fantke, P., Jolliet, O., 2016. Stochastic modeling of near-field
645 exposure to parabens in personal care products. J. Expo. Sci. Environ. Epidemiol.
646 doi:10.1038/jes.2015.85
647 Dancik, Y., Miller, M.A., Jaworska, J., Kasting, G.B., 2013. Design and performance of a
648 spreadsheet-based model for estimating bioavailability of chemicals from dermal
649 exposure. Adv. Drug Deliv. Rev., Modeling the human skin barrier - Towards a better
650 understanding of dermal absorption 65, 221–236. doi:10.1016/j.addr.2012.01.006
651 Delmaar, C., Bokkers, B., ter Burg, W., Schuur, G., 2014. Validation of an aggregate
652 exposure model for substances in consumer products: a case study of diethyl phthalate
653 in personal care products. J. Expo. Sci. Environ. Epidemiol. 1–7.
654 doi:10.1038/jes.2014.68
655 Delmaar, J.E., Park, M.V.D.Z., van Engelen, J.G.M., 2005. ConsExpo 4.0, Consumer
656 Exposure and Uptake Models, Program Manual.
657 Dionisio, K.L., Frame, A.M., Goldsmith, M.-R., Wambaugh, J.F., Liddell, A., Cathey, T.,
658 Smith, D., Vail, J., Ernstoff, A.S., Fantke, P., Jolliet, O., Judson, R.S., 2015.
659 Exploring consumer exposure pathways and patterns of use for chemicals in the
660 environment. Toxicol. Rep. 2, 228–237. doi:10.1016/j.toxrep.2014.12.009
661 Dudzina, T., Delmaar, C.J.E., Biesterbos, J.W.H., Bakker, M.I., Bokkers, B.G.H., Scheepers,
662 P.T.J., van Engelen, J.G.M., Hungerbuehler, K., von Goetz, N., 2015a. The
663 probabilistic aggregate consumer exposure model (PACEM): Validation and
664 comparison to a lower-tier assessment for the cyclic siloxane D5. Environ. Int. 79, 8–
665 16. doi:10.1016/j.envint.2015.03.006
666 Dudzina, T., Garcia Hidalgo, E., von Goetz, N., Bogdal, C., Hungerbuehler, K., 2015b.
667 Evaporation of decamethylcyclopentasiloxane (D5) from selected cosmetic products:
668 Implications for consumer exposure modeling. Environ. Int. 84, 55–63.
669 doi:10.1016/j.envint.2015.07.013
670 European Union, 2009. Regulation (EC) No. 1223/2009 of the European parliament and of
671 the council of 30 November 2009 on cosmetic products (recast).
672 Flynn, G.L., 1990. Physicochemical determinants of skin absorption, in: Gerrity, T.R., Henry,
673 C.J. (Eds.), Principles of Route-To-Route Extrapolation for Risk Assessment.
674 Elsevier.
675 Gavazzoni Dias, M.F.R., de Almeida, A.M., Cecato, P.M.R., Adriano, A.R., Pichler, J., 2014.
676 The Shampoo pH can Affect the Hair: Myth or Reality? Int. J. Trichology 6, 95–99.
677 doi:10.4103/0974-7753.139078
678 Goldsmith, M.-R., Grulke, C.M., Brooks, R.D., Transue, T.R., Tan, Y.M., Frame, A.,
679 Egeghy, P.P., Edwards, R., Chang, D.T., Tornero-Velez, R., Isaacs, K., Wang, A.,
680 Johnson, J., Holm, K., Reich, M., Mitchell, J., Vallero, D.A., Phillips, L., Phillips, M.,
681 Wambaugh, J.F., Judson, R.S., Buckley, T.J., Dary, C.C., 2014. Development of a
682 consumer product ingredient database for chemical exposure screening and
683 prioritization. Food Chem. Toxicol. 65, 269–279. doi:10.1016/j.fct.2013.12.029
684 Grégoire, S., Ribaud, C., Benech, F., Meunier, J. r., Garrigues-Mazert, A., Guy, R. h., 2009.
685 Prediction of chemical absorption into and through the skin from cosmetic and

686 dermatological formulations. Br. J. Dermatol. 160, 80–91. doi:10.1111/j.1365-
687 2133.2008.08866.x
688 Hadgraft, J., 2002. Transdermal Drug Delivery Systems: Revised And Expanded. CRC Press.
689 Hall, B., Tozer, S., Safford, B., Coroama, M., Steiling, W., Leneveu-Duchemin, M.C.,
690 McNamara, C., Gibney, M., 2007. European consumer exposure to cosmetic products,
691 a framework for conducting population exposure assessments. Food Chem. Toxicol.
692 45, 2097–2108. doi:10.1016/j.fct.2007.06.017
693 Hauschild, M.Z., Huijbregts, M., Jolliet, O., Macleod, M., Margni, M., van de Meent, D.,
694 Rosenbaum, R.K., McKone, T.E., 2008. Building a Model Based on Scientific
695 Consensus for Life Cycle Impact Assessment of Chemicals: The Search for Harmony
696 and Parsimony. Environ. Sci. Technol. 42, 7032–7037. doi:10.1021/es703145t
697 Isaacs, K.K., Glen, W.G., Egeghy, P., Goldsmith, M.-R., Smith, L., Vallero, D., Brooks, R.,
698 Grulke, C.M., Özkaynak, H., 2014. SHEDS-HT: An Integrated Probabilistic Exposure
699 Model for Prioritizing Exposures to Chemicals with Near-Field and Dietary Sources.
700 Environ. Sci. Technol. 48, 12750-12759. doi:10.1021/es502513w
701 Jolliet, O., Ernstoff, A.S., Csiszar, S.A., Fantke, P., 2015. Defining Product Intake Fraction to
702 Quantify and Compare Exposure to Consumer Products. Environ. Sci. Technol. 49,
703 8924-8931. doi:10.1021/acs.est.5b01083
704 Jolliet, O., Fantke, P., 2015. Human Toxicity, in: Hauschild, M.Z., Huijbregts, M.A.J. (Eds.),
705 Life Cycle Impact Assessment, LCA Compendium – The Complete World of Life
706 Cycle Assessment. Springer Netherlands, Dordrecht, pp. 75–96.
707 Kasting, G.B., Miller, M.A., 2006. Kinetics of finite dose absorption through skin 2: Volatile
708 compounds. J. Pharm. Sci. 95, 268–280. doi:10.1002/jps.20497
709 Koch, H.M., Aylward, L.L., Hays, S.M., Smolders, R., Moos, R.K., Cocker, J., Jones, K.,
710 Warren, N., Levy, L., Bevan, R., 2014. Inter- and intra-individual variation in urinary
711 biomarker concentrations over a 6-day sampling period. Part 2: Personal care product
712 ingredients. Toxicol. Lett., Advances in Biological Monitoring for Occupational and
713 Environmental Health - II 231, 261–269. doi:10.1016/j.toxlet.2014.06.023
714 Koehler, A., Wildbolz, C., 2009. Comparing the Environmental Footprints of Home-Care and
715 Personal-Hygiene Products: The Relevance of Different Life-Cycle Phases. Environ.
716 Sci. Technol. 43, 8643–8651. doi:10.1021/es901236f
717 Kolpin, D.W., Furlong, E.T., Meyer, M.T., Thurman, E.M., Zaugg, S.D., Barber, L.B.,
718 Buxton, H.T., 2002. Pharmaceuticals, Hormones, and Other Organic Wastewater
719 Contaminants in U.S. Streams, 1999−2000: A National Reconnaissance. Environ.
720 Sci. Technol. 36, 1202–1211. doi:10.1021/es011055j
721 Lian, G., Chen, L., Han, L., 2008. An evaluation of mathematical models for predicting skin
722 permeability. J. Pharm. Sci. 97, 584–598. doi:10.1002/jps.21074
723 Loretz, L., Api, A.M., Barraj, L., Burdick, J., Davis, D.A., Dressler, W., Gilberti, E., Jarrett,
724 G., Mann, S., Laurie Pan, Y.H., Re, T., Renskers, K., Scrafford, C., Vater, S., 2006.
725 Exposure data for personal care products: Hairspray, spray perfume, liquid
726 foundation, shampoo, body wash, and solid antiperspirant. Food Chem. Toxicol. 44,
727 2008–2018. doi:10.1016/j.fct.2006.06.029
728 McKone, T.E., Bogen, K.T., 1992. Uncertainties in health-risk assessment: An integrated
729 case study based on tetrachloroethylene in California groundwater. Regul. Toxicol.
730 Pharmacol. 15, 86–103. doi:10.1016/0273-2300(92)90087-P

731 Megrab, N.A., Williams, A.C., Barry, B.W., 1995. Oestradiol permeation through human
732 skin and silastic membrane: effects of propylene glycol and supersaturation. J.
733 Controlled Release 36, 277–294. doi:10.1016/0168-3659(95)00062-D
734 Moser, K., Kriwet, K., Naik, A., Kalia, Y.N., Guy, R.H., 2001. Passive skin penetration
735 enhancement and its quantification in vitro. Eur. J. Pharm. Biopharm. 52, 103–112.
736 doi:10.1016/S0939-6411(01)00166-7
737 Pal, A., He, Y., Jekel, M., Reinhard, M., Gin, K.Y.-H., 2014. Emerging contaminants of
738 public health significance as water quality indicator compounds in the urban water
739 cycle. Environ. Int. 71, 46–62. doi:10.1016/j.envint.2014.05.025
740 Rosenbaum, R.K., Bachmann, T.M., Gold, L.S., Huijbregts, M.A.J., Jolliet, O., Juraske, R.,
741 Koehler, A., Larsen, H.F., MacLeod, M., Margni, M., McKone, T.E., Payet, J.,
742 Schuhmacher, M., Meent, D., Hauschild, M.Z., 2008. USEtox—the UNEP-SETAC
743 toxicity model: recommended characterisation factors for human toxicity and
744 freshwater ecotoxicity in life cycle impact assessment. Int. J. Life Cycle Assess. 13,
745 532–546. doi:10.1007/s11367-008-0038-4
746 Rosenbaum, R.K., Meijer, A., Demou, E., Hellweg, S., Jolliet, O., Lam, N.L., Margni, M.,
747 McKone, T.E., 2015. Indoor Air Pollutant Exposure for Life Cycle Assessment:
748 Regional Health Impact Factors for Households. Environ. Sci. Technol. 49, 12823–
749 12831. doi:10.1021/acs.est.5b00890
750 Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C.,
751 O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an
752 aggregate exposure model to estimate consumer exposure to fragrance ingredients in
753 personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
754 doi:10.1016/j.yrtph.2015.05.017
755 Shin, H.-M., Ernstoff, A.S., Arnot, J.A., Wetmore, B., Csiszar, S.A., Fantke, P., Zhang, X.,
756 McKone, T.E., Jolliet, O., Bennett, D.H., 2015. Risk-based High-Throughput
757 Chemical Screening and Prioritization using Exposure Models and in Vitro
758 Bioactivity Assays. Environ. Sci. Technol. 49, 6760–6771.
759 doi:10.1021/acs.est.5b00498
760 Tadros, T., Izquierdo, P., Esquena, J., Solans, C., 2004. Formation and stability of nano-
761 emulsions. Adv. Colloid Interface Sci., Emulsions, From Fundamentals to Practical
762 Applications 108–109, 303–318. doi:10.1016/j.cis.2003.10.023
763 US-EPA United States - Environmental Protection Agency, 2012. Estimation Programs
764 Interface SuiteTM for Microsoft® Windows, v 4.11.
765 Wambaugh, J.F., Setzer, R.W., Reif, D.M., Gangwal, S., Mitchell-Blackwood, J., Arnot, J.A.,
766 Jolliet, O., Frame, A., Rabinowitz, J., Knudsen, T.B., Judson, R.S., Egeghy, P.,
767 Vallero, D., Cohen Hubal, E.A., 2013. High-Throughput Models for Exposure-Based
768 Chemical Prioritization in the ExpoCast Project. Environ. Sci. Technol. 47, 8479-
769 8488. doi:10.1021/es400482g
770 Wenger, Y., Li, D., Jolliet, O., 2012. Indoor intake fraction considering surface sorption of air
771 organic compounds for life cycle assessment. Int. J. Life Cycle Assess. 17, 919–931.
772 doi:10.1007/s11367-012-0420-0
773 Wetmore, B.A., Wambaugh, J.F., Allen, B., Ferguson, S.S., Sochaski, M.A., Setzer, R.W.,
774 Houck, K.A., Strope, C.L., Cantwell, K., Judson, R.S., LeCluyse, E., Clewell, H.J.,
775 Thomas, R.S., Andersen, M.E., 2015. Incorporating High-Throughput Exposure
776 Predictions with Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical
777 Toxicity Testing. Toxicol. Sci. 148, 121–136. doi:10.1093/toxsci/kfv171

Williams, A.C., Barry, B.W., 2012. Penetration enhancers. Adv. Drug Deliv. Rev., MOST CITED PAPERS IN THE HISTORY OF ADVANCED DRUG DELIVERY REVIEWS: A TRIBUTE TO THE 25TH ANNIVERSARY OF THE JOURNAL 64, Supplement, 128–137. doi:10.1016/j.addr.2012.09.032

Williams, F., 2004. EDETOX. Evaluations and predictions of dermal absorption of toxic chemicals. Int. Arch. Occup. Environ. Health 77, 150–151. doi:10.1007/s00420-003-0484-z

Wilschut, A., ten Berge, W.F., Robinson, P.J., McKone, T.E., 1995. Estimating skin permeation. The validation of five mathematical skin permeation models. Chemosphere 30, 1275–1296. doi:10.1016/0045-6535(95)00023-2

Won, D., Corsi, R.L., Rynes, M., 2001. Sorptive Interactions between VOCs and Indoor Materials. Indoor Air 11, 246–256. doi:10.1034/j.1600-0668.2001.110406.x